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Evaluation of ceftazidime-avibactam susceptibility in carbapenem resistant *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* isolates

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ABSTRACT

Aims: Carbapenem-resistant Gram-negative microorganisms are gradually increasing in hospitalized patients in intensive care units and causes increased morbidity, mortality, and cost. This study aims to investigate the susceptibility of ceftazidime-avibactam (caz-avi), which has recently started to be used for the treatment of infections caused by carbapenem-resistant (CR) Gram-negative bacteria isolated from various samples received from the intensive care unit (ICU) of our hospital.

Methods: Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) strains isolated from various clinical specimens that were sent to our laboratory between January 1st, 2021, and October 30th, 2022, were retrospectively evaluated in the study. The culture and antibiogram results of the samples were received over the laboratory information system (LIS) and evaluated using statistical analyses. Ceftazidime-avibactam susceptibility was studied using the disc diffusion method.

Results: Ceftazidime-avibactam antibiotic susceptibility test results of 352 (69.4%) CRKP and 155 (30.6%) CRPA strains isolated from various clinical samples from the ICU of our hospital were analyzed. Of the CRKP strains, 313 (88.9%) were found to be susceptible and 39 (11.1%) were found to be resistant to ceftazidime-avibactam. Of the CRPA strains, 131 (84.5%) were found to be susceptible and 24 (15.5%) were found to be resistant.

Conclusion: Determining the regional susceptibility of carbapenem-resistant strains isolated in our hospital to a new antimicrobial combination such as caz-avi will allow a better understanding of the spread of resistance.

Keywords: Ceftazidime-avibactam, antimicrobial resistance, Gram negative bacteria

INTRODUCTION

Today, carbapenems are used as a last step in the treatment of infections caused by multi-drug resistant (MDR) Gram-negative microorganisms. The frequency of carbapenem-resistant Gram-negative microorganisms in the ICU is increasing, causing higher morbidity and mortality rates.[1,2] In recent years, polymyxin group antibiotics have been widely used in the treatment of infections caused by CR Gram-negative microorganisms. Polymyxin group antibiotics have an optimal effect in treatment but they have inevitable toxic adverse effects.[3] Fosfomycin, tigecycline, and aminoglycoside antibiotics are also used in the treatment of CR.[4] In addition to the increasing carbapenem resistance, the limited number of currently available antibiotics and their toxic adverse effects have led to an increase in research on antibiotic options. In general, research has focused on caz-avi, meropenem-vaborbactam, ceftolozane-vaborbactam, imipenem/cilastatin-relebactam, eravacycline, plazomycin, and cefiderecol antibiotics.[1]

Avibactam is a diazobicyclooctane beta-lactamase inhibitor that has recently come into use in clinical practice and has expanded the spectrum of ceftazidime including many carbapenem-resistant *Enterobacteriaceae* members and *Pseudomonas aeruginosa (P. aeruginosa)*.[1] Its combination with ceftazidime was approved by the United States Food and Drug Administration (FDA) for intra-abdominal infections and complicated urinary tract infections in 2015 and it also began to be used for hospital-acquired and ventilator-associated pneumonia (VIP) in 2018.[5] Ceftazidime-avibactam is a potential new agent in the treatment of infections caused by MDR microorganisms.[6]

In general, antibiotic resistance rates show regional differences.[1] Ceftazidime-avibactam susceptibility rates of CR strains in the ICU of our hospital will contribute to regional data and will guide the planning of treatment. This study aimed to investigate the susceptibility rates of a new combination caz-avi in CR strains isolated from the ICU of our hospital.

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METHODS

The study was performed with the permission of Antalya Training and Research Hospital Ethics Committee (Date: 06.01.2022, Decision No: 1/8). All procedures were conducted in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Carbapenem-resistant *Klebsiella pneumoniae (K. pneumoniae)* (n=352) and carbapenem-resistant *P. aeruginosa* (n=155) strains isolated from various clinical specimens, sent from the ICU to our laboratory between January 1st, 2021, and October 30th, 2022, were included in the study. The culture and antibiogram results of the samples taken from the LIS were statistically evaluated. Gram staining was performed on each sample sent to the laboratory during routine culture procedures. Samples were inoculated onto 5% sheep blood agar (BA) (RTA, Turkey), chocolate agar (CA) (RTA, Turkey) and eosin methylene blue agar (EMB) (RTA, Turkey) and incubated at 37°C for 18-24 hours. Identification of isolates was performed using matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Biomerieux, France) in our routine studies and antibiotic susceptibility tests were performed using the VITEK 2 (Biomerieux, France) system in line with the recommendations of the manufacturers. The VITEK 2 system was used to determine carbapenem resistance. Ceftazidime-avibactam susceptibility was studied using the disc diffusion method. CRPA and CRKP colonies were inoculated onto Müller-Hinton agar (RTA, Turkey) at 0.5 McFarland dilution to detect caz-avi susceptibility. Ceftazidime-avibactam (30 µg/10 µg) discs were placed and incubated at 37°C for 18-24 hours. Diameters of the non-growth zone around the antibiotic discs were measured and sensitivities were evaluated according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria. *P. aeruginosa* ATCC 27853 and *K. pneumoniae* 700603 (ESBL) were used as control strains.

Statistical Analysis

The Statistical Packages for the Social Sciences (SPSS) software version 22.0 (SPSS Inc., Chicago, USA) was used for statistical analysis of the study.

RESULTS

In total, 352 CRKP and 155 CRPA strains were isolated from various clinical samples sent to the laboratory from the ICUs of our hospital. The age of the patients from whom the isolates were obtained was between 18 and 86 years. Two hundred four (58.0%) patients who had CRKP strains were male and 148 (42.0%) were female. One hundred four (67.0%) patients who had CRPA isolates were male and 51 (33.0%) were female. Carbapenem-resistant *K. pneumoniae* isolates were received from the general ICU (n=278, 79.0%), the surgical ICU (n=32, 9.0%), the neurologic ICU (n=29, 8.0%), and the coronary ICU (n=13, 4.0%), respectively. Carbapenem-resistant *P. aeruginosa* isolates were received from the general ICU (n=123, 79.3%), the surgical ICU (n=20, 13.0%), the neurologic ICU (n=10, 6.4%), and the coronary ICU (n=2, 1.3%), respectively. Three-hundred-fifty-two CRKP strains were isolated from blood (46%), sputum/BAL (41.5%), urine (7.7%), and tissue/abscess/wound samples (4.8%). One-hundred-fifty-five CRPA strains were isolated from blood (12.3%), sputum/BAL (69.0%), urine (16.1%), tissue/abscess/wound samples (2.6%) (Table 1).

Susceptibilities to amikacin, gentamicin, ciprofloxacin, meropenem and imipenem in CRKP isolates were determined as follows: 41 (11.6%), 32 (9.1%), 1 (0.3%), 5 (1.5%) and 3 (0.9%), respectively. All CRKP isolates showed resistance to amoxicillin clavulonic acid, cefepime, levofloxacin, phosphomycin, and ertapenem. Amikacin, meropenem and imipenem susceptibilities in CRPA isolates were determined as 95 (61.3%), 58 (37.5%) and 2 (1.3%), respectively. All CRPA isolates were found to be resistant to aztreonam, gentamicin, piperacillin, cefepime and ciprofloxacin (Table 2).

Of the CRKP strains, 313 (88.9%) were found to be susceptible and 39 (11.1%) were found to be resistant to ceftazidime-avibactam. Of the CRPA strains, 131 (84.5%) were found to be susceptible and 24 (15.5%) were found to be resistant. The caz-avi resistance rates of CRKP and CRPA strains isolated from tissue/abscess/wound samples were determined as 29.4% and 25.0%, respectively. It was statistically significantly higher than all other samples (CRKP p=0.05 and CRPA p=0.005).

Table 1. Sample distribution and caz-avi susceptibility results in CRKP and CRPA isolates

Sample	CRKP (n:352)			CRPA (n:155)		
	Sensitive n (%)	Resistant n (%)	P value	Sensitive n (%)	Resistant n (%)	P value
Blood	147 (89.8)	15 (10.2)	<0.05	16 (84.2)	3 (15.8)	<0.005
Sputum/BAL	132 (90.5)	14 (9.5)		91 (85.1)	16 (14.9)	
Urine	22 (81.5)	5 (18.5)		21 (84.0)	4 (16.0)	
Tissue/abscess/wound	12 (70.6)	5 (29.4)		3 (75.0)	1 (25.0)	
Total	313 (88.9)	39 (11.1)		131 (84.7)	24 (15.3)	

CRKP: Carbapenem-resistant *Klebsiella pneumoniae*. CRPA: Carbapenem-resistant *Pseudomonas aeruginosa*.

Table 2. Antibiotic susceptibility rates in CRKP and CRPA isolates

Anti-Bacterial Agent	CRKP (69.4%) n: 352		CRPA (30.6%) n: 155	
	Sensitive n (%)	Resistant n (%)	Sensitive n (%)	Resistant n (%)
Amikacin	41 (11.6)	311 (88.4)	95 (61.3)	60 (38.7)
Aztreonam	N*	N*	-	155 (100)
Gentamicin	32 (9.1)	320 (90.9)	-	155 (100)
Piperacillin	N*	N*	-	155 (100)
Amoxicillin Clavulonic Acid	-	352 (100)	N*	N*
Cefepime	-	352 (100)	-	155 (100)
Ceftazidime Avibactam	313 (88.9)	39 (11.1)	131 (84.5)	24 (15.5)
Ciprofloxacin	1 (0.3)	351 (99.7)	-	155 (100)
Levofloxacin	-	352 (100)	N*	N*
Fosfomycin	-	352 (100)	N*	N*
Meropenem	5 (1.5)	347 (98.5)	58 (37.5)	97 (62.5)
İmipenem	3 (0.9)	349 (99.1)	2 (1.3)	153 (98.7)
Ertapenem	-	352 (100)	N*	N*
Trimethoprim/Sulfomethoxazole	43 (12.2)	309 (87.8)	N*	N*

N*: Not worked, CRKP: Carbapenem-resistant *Klebsiella pneumoniae*. CRPA: Carbapenem-resistant *Pseudomonas aeruginosa*.

DISCUSSION

In the ICU, carbapenem-resistant Gram-negative bacteria infections have limited treatment options and high morbidity and mortality rates.[7,8] Ceftazidime is a third-generation cephalosporin with a broad spectrum of antimicrobial activity. The usefulness of cephalosporin in treating infections has been limited due to the spread of cephalosporin resistance through mechanisms such as ESBL production. Combining ceftazidime with avibactam, a novel β-lactamase inhibitor in diazobicyclooctane structure has increased its in vitro activity against several β-lactamase-producing aerobic Gram-negative pathogens. On the other hand, the addition of avibactam has been shown to restore the in vitro activity of ceftazidime against many extended spectrum β-lactamase, AmpC, KPC, and OXA-48-producing *Enterobacteriaceae* and CRPA isolates. In the INFORM global surveillance program from 2012-2014, 99.5% of *Enterobacteriaceae* and 92.0% of *P. aeruginosa* isolates were susceptible to caz-avi.[9] With the recent approval of its use in our country, concordant with global data, resistance to caz-avi antibiotherapy has begun to be reported in many studies and case reports.[10,11] In this study, caz-avi and other antibiotic susceptibilities of CRKP and CRPA strains in patients hospitalized in ICUs are presented to reveal regional data.

Recent global observations indicate an increase in resistance to ceftazidime avibactam for *K. pneumoniae* and *P. aeruginosa* isolates, despite previous studies abroad showing high susceptibility (95%-99%).[11,12] Sader et al.[13] evaluated the antimicrobial susceptibility of 623 Gram-negative organism-caused infections in patients with cancer in 52 hospitals in the United States of America as part of the INFORM program between 2013 and 2014 and found all *Enterobacteriaceae* 100% susceptible to caz-avi. In the same study, caz-avi sensitivities in *P. aeruginosa* strains were reported as 96.6%. Different from Sader et al.[13] carbapenem-resistant *P. aeruginosa* strains (n=131) were included in our study and caz-avi susceptibility was 84.5% in CRPA strains. Kempf et al.[14] found caz-avi resistance rate of 19.6% in carbapenem resistant *K. pneumoniae* isolates from respiratory tract specimens, while in the study conducted by Ramadan et al.[15] the resistance rate reached 79% in *K. pneumoniae* isolates. In a study by Torrens et al.16 with *P. aeruginosa* obtained from ICU of 11 different countries, including Turkey, it was observed that caz-avi resistance increased to 83% in MDR strains.

Livermore et al.[17] found the caz-avi susceptibility rate as 95% in *Enterobacteriaceae*. In their study, *Enterobacteriaceae* strains containing the most OXA-48 (36.7%), KPC, and NDM were isolated and almost all isolates with metallo beta-lactamase were reported as resistant to caz-avi. In the same study, caz-avi was found to be effective against *P. aeruginosa* in which AmpC was not suppressed and no effect was detected against strains with efflux-mediated resistance. In a multicenter study covering Europe, Latin America, and Asian-Pacific countries, Castenheria et al.[18] found caz-avi susceptibility rates of 78.7% in 286 CR strains. In the same study, non-metallo beta-lactamase CR strains were reported as 100% susceptible. Although carbapenemase resistance genes were not identified in our study, it is important in terms of reporting the first resistance data for caz-avi from our region.

Sensitivity studies started to be reported in our country with the license of caz-avi in 2019. In a multicenter study conducted in our country, İşler et al.[19] determined that 71% of OXA–48–like CRKP strains isolated from 200 blood cultures were susceptible to caz-avi. Mirza et al.[20] reported caz-avi susceptibility as 83.3% in 102 CRPA strains isolated from various clinical samples. Öztaş et al.[10] reported caz-

avi susceptibility as 77.5% in CRKP strains isolated from various clinical samples between 2017 and 2021. These susceptibility rates were low when compared with our data. In Öztaş et al.[10] study, the highest sensitivity was reported for colistin (83.26%) but it was recommended to be considered as a last option due to its nephrotoxicity. In another study, caz-avi and colistin susceptibilities of CRPA strains were determined as 90% and 100%, respectively, between 2016 and 2021.21 Arıcı et al.[11] investigated the invitro efficacy of caz-avi against CRKP and CRPA isolates isolated from ICUs as the causative agents of VIP and found the resistance rates to be 22.2% and 86.4%, respectively. The results of this study, in which high resistance rates were reported from our country, are alarming. The authors of this study emphasized the significance of performing regular surveillance cultures to control infections in the ICU. They also highlighted the need for frequent monitoring of resistance to ensure the timely and effective use of ceftazidime-avibactam, which is one of the last-resort antibiotics for severe infections in the ICU. It is expected that patients who have been hospitalized in the ICU for a long period of time and those with poor general condition will be expected to show resistance to newly introduced antibiotics. Our study revealed that caz-avi sensitivity was relatively high, despite selecting CRPA and CRKP isolates from ICU units.

In our study, we found that the rates of resistance to CRKP and CRPA in abscess and wound cultures were 29.4% and 25.0%, respectively, which was statistically significantly higher than in all other samples (CRKP p=0.05 and CRPA p=0.005). In certain clinical studies, the effectiveness of treating caz-avi susceptible strains was evaluated based on the diversity of the samples. Unlike other samples, some studies found that tissue and abscess cultures had response rates to treatment as low as 50.0%.[22,23]

Yang et al.[24] reported a caz-avi sensitivity of 65.5% in a total of 133 isolated CRKP strains. The authors emphasized that the disc diffusion method was a good alternative as an economical and practical method to detect the antibacterial activity of caz-avi against *Enterobacteriaceae* because automatic antimicrobial susceptibility test cards were not available in 2019 for caz-avi. Likewise, İşler et al.[19] studied caz-avi sensitivities in vitro using Sensititre, Etest, and 10/4 µg disc methods and found the results to be compatible. Also, they stated that the disc diffusion method was recommendable.

Our study has some limitations. The small number of patients and isolates that underwent susceptibility testing with ceftazidime-avibactam and the lack of investigation of resistance genes can be counted among these limitations. In addition, it could not be determined whether the patients with resistance strains in our study had previously used caz avi. It should also be taken into consideration that our results regarding caz-avi resistance may not reflect the whole region since our study was single-centered. One of the critical steps in preventing resistance to antibiotics is monitoring the resistance. Therefore, data collected from similar studies at a local and regional level will aid in understanding the spread of resistance.

CONCLUSION

Antimicrobial resistance is a dynamic and rapidly developing field. The treatment of resistant patients will increasingly be a challenge for physicians.[25] In our country, the use of caz-avi has only been authorized for complicated cases hospitalized in the ICU since 2019.[26] It is important to evaluate clinical success for appropriate patient groups in randomized controlled studies, based on in vitro studies conducted in our country for resistant infections. Maintaining active surveillance studies together with the meticulous implementation of appropriate antibiotic use policies will allow to ensure control of antibiotic resistance.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Antalya Training and Research Hospital Ethics Committee (Date: 01.012022, Decision No: 2022-006- 1/8).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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